55. (New) An isolated nucleic acid comprising a nucleotide sequence encoding an NGSP polypeptide, which is a polypeptide of a *Neisseria* species with the proviso that said *Neisseria* species is not *N. meningitidis*, which polypeptide has a molecular weight of about 40 kD to about 55 kD as determined in SDS polyacrylamide gel electrophoresis using glutamic dehydrogenase, carbonic anhydrase and myoglobin-blue as molecular weight markers and which polypeptide has a serine protease motif.--.

REMARKS

Objection to Specification

The text of the specification has been amended merely to avoid certain informalities regarding the hyperlinks. Hence, as amended the specification avoids the objection to the specification in the Office Action. In addition, the specification is amended at page 3, line 15 to correct an obvious editorial error by replacing the term "TBLASTN" with the term "BLASTP." Such error would be obvious to one skilled in the art, particularly in view of the teaching of the specification at page 9, lines 12-28. No new matter is added. In light of the amendments, it is submitted that the objection to the specification is avoided and should be withdrawn.

Applicants respectfully acknowledge the indication that claims 38 and 49 are allowed. Claim 38 is amended herein to recite the term "nucleic acid comprising" instead of the less conventional "DNA having." This recitation is fully supported by the specification, e.g. at page 4, lines 19-22, etc. and is more consistent with the language of the other pending claims.

Upon entry of the present amendments, claims 37-39 and 48-55 will be pending. New claim 54, directed to a nucleic acid encoding a fragment of an NGSP, has the same limitations as allowed claim 48, with the sole exception that it specifies that the fragment comprises "at least 8 amino acids." This claim is fully supported by he specification, e.g., at page 12, line 1; and in light of the allowance of claim 48, is directed to allowable subject matter.

New claim 55, directed to an isolated nucleic acid encoding an NGSP polypeptide of a *Neisseria* species with the proviso that said *Neisseria* species is not *N. meningitidis*, which polypeptide has a molecular weight of about 40 kD to about 55 kD as determined in SDS polyacrylamide gel electrophoresis using glutamic dehydrogenase, carbonic anhydrase and myoglobin-blue as molecular weight markers, further recites that the polypeptide "has a serine protease motif." Support for this recitation is found in the specification, e.g., at page 41, line 26 through page 42, line 2.

Withdrawal of claim 53

In paragraph 2 of the Office Action, claim 53 is indicated as being drawn to a non-elected invention.

Claim 53 is drawn to a method of producing an NGSP polypeptide comprising culturing a host cell with a vector comprising the nucleic acid of claim 37, 38, 39 or 40. No explanation was given for the withdrawal of claim 53. Since claim 53 is drawn to a method of using the nucleic acid that is under examination, no additional search is required to examine claim 53 and it would not be an undue burden to examine claim 53. Additionally, Applicants respectfully note that claim 38 is allowed and that, in view of *In re Ochiai*, 71 F.3d 1565 (Fed.Cir. 1995), it is PTO policy (see 1184 OG86 (March 26, 1996)) that if a product is deemed allowable, Applicants may request that methods of using or making that

product be rejoined if Examiner has restricted the methods of using or making a product from the product. Therefore, Applicants respectfully request that claim 53 be rejoined to claims 37-39 and 48-52 and new claims 54-55.

In view of the above, it is submitted that, upon entry of the above amendments, claims 37-39 and 48-55 should be pending and under active consideration, although claims 38 and 48 are allowed.

Objections to Figures

The figures are objected to for reasons noted by the Draftsperson.

In response, a photocopy of the formal figures to be submitted upon allowance is submitted herewith and it is respectfully requested that this objection be withdrawn.

Section 112, 2d Paragraph

Claims 37, 39 and 50-52 are rejected as indefinite in the use of abbreviations.

In accord with the suggestion, claim 37 (and hence claims 39 and 50-52 dependent thereon) is amended to recite the full terminology at first occurrence with the abbreviated recitation in parenthesis. Accordingly, this rejection is avoided and should be withdrawn.

Section 112, 1st Paragraph

Claim 39 is rejected as not supported by the recitation "1 mm NaCl." The Office Action notes that the specification at page 25, lines 5-9 supports the recitation "0.25 M NaCl."

Accordingly, claim 39 is amended to recite the proper salt concentration taught in the specification. Thus, this rejection is avoided and should be withdrawn.

Section 102

Claims 37 and 50-52 are rejected under 35 USC 102(e) as allegedly anticipated by U.S. Patent No. 6,096,529 to Gilbert et al. (Gilbert). It is alleged that Gilbert teaches an isolated nucleotide sequence and isolated polypeptide of *Neisseria gonorrhoeae* having a molecular weight of about 40 kD as measured by SDS-PAGE.

Attorneys for Applicants emphatically disagree and submit that this rejection is in error.

In order to more clearly point out and distinctly claim the novel nucleic acid of claim 37 (and claims 50-52 to the extent dependent thereon), claim 37 is amended herein to recite that the polypeptide encoded by the isolated *Neisseria* nucleic acid "has about 36% sequence identify to Deg P protein of *E. coli* when % sequence is determined using a BLASTP program using FASTA formal, expect 10 filter default, description 100." Such recitation is fully supported by the present specification in the "Summary of the Invention", at page 3, lines 13-17; see also, at page 41, line 25 through page 42, line 2.

Applicants have conducted BLASTP comparisons between the polypeptides encoded by the polynucleotides isolated from *Neisseria meningitis* or *N. gonorrhea* described by Gilbert and the Deg P polypeptide of *E. coli*, the sequence of which is publicly available from Ncbi (see Swiss Prot print out attached as part of Exhibit 1, in particular Reference 7 by Lipinska et al., J. Bacteriol 172(4): 1741-97 (1990) regarding Deg P (copy attached as part of Exhibit 1)). The polynucleotides of Gilbert are taught to hybridize under stringent conditions to SEQ ID Nos. 1 or 3 (Gilbert SEQ ID Nos. 1 and 3), which, respectively encode

polypeptides designated SEQ ID Nos. 2 and 4 (Gilbert SEQ ID Nos. 2 and 4). As indicated at Gilbert col. 5, lines 61-63, hybridization under stringent condition means that a molecule "will hybridize to its target substance, but to no other sequences." Results of the BLASTP comparisions are shown in Exhibit 1, Parts A and B submitted herewith.

As shown in Exhibit 1, Part A, there was no similarity between the sequence of the polypeptide encoded by the polypeptide having Gilbert SEQ ID No. 4 and the Deg P polypeptide of *E. coli*. As shown in Exhibit 1, Part B, there was no sequence similarity between the polypeptide encoded by Gilbert SEQ ID No. 2 and the Deg P polypeptide of *E. coli*.

In complete contrast, as taught in the present application, (see page 3, lines 13-18) and as recited in claim 37, the polypeptide encoded by the presently claimed nucleic acid is at least about 36% sequence identity to the Deg P polypeptide of *E. coli*. See also Exhibit 2, Part A, submitted herewith, which presents results of a BLAST comparison between the polypeptide encoded by the presently claimed nucleic acid and that encoded by Deg P polypeptide of *E. coli*. As identified in Exhibit 2, Part A, there is about 43% sequence identity between the polypeptide encoded by the nucleic acid of present claim 37 and the Deg P polypeptide of *E. coli*.

In view of the significant difference demonstrated, it is submitted that the rejection based on claim 37 is in error and must be withdrawn.

Further attention is directed to new claim 55 added by amendment herein. New claim 55 recites that the novel isolated nucleic acid of *Neisseria* at this claim encodes a polypeptide having a serine protease motif. Applicants have conducted BLAST comparisons to determine whether the polypeptide encoded by the polynucleotide described by Gilbert has

a serine protease motif (HDS). Results are shown in Exhibit 1, Parts C and D submitted herewith.

As shown in Exhibit 1, Part C, there was no conserved serine protease motif in the polypeptide encoded by the polynucleotide designated Gilbert SEQ ID No. 4 when compared with the serine protease motif contained in Deg P polypeptide of *E. coli*.

As shown in Exhibit 1, Part D, there was no conserved serine protease motif in the polypeptide encoded by the polynucleotide designated Gilbert SEQ ID No. 2 when compared with the serine protease motif contained in the Deg P polypeptide of *E. coli*.

In complete contrast, as taught in the present application (see page 41, line 25 through page 42, line 2) and as recited in claim 55, the polypeptide encoded by the presently claimed nucleic acid has a serine protease motif as found in the Deg P polypeptide *E. coli*. See also Exhibit 2, Part B, submitted herewith, which presents results of a BLAST search for a serine protease motif in the amino acid encoded by the nucleic acid of the present claim 55 and of the nucleic acid encoding Deg P polypeptide of *E. coli*.

In view of the above significant difference demonstrated, it is respectfully submitted that the novel nucleic acid of claim 55 is also not anticipated by the Gilbert reference.

For all the above reasons, it is submitted that this rejection based on Section 102 must be withdrawn.

Claim 48 is rejected under Section 102(b) as anticipated by Zheng et al., 1996, Genetics 143: 941-52 (Zheng). The Office Action asserts that Zheng discloses an isolated nucleic acid comprising at least 21 contiguous nucleotides having 100% sequence identity with a fragment of the presently recited SEQ ID No. 3. Further, the Office Action asserts that

the Zheng nucleic acid inherently encodes a polypeptide comprising at least 7 amino acids which constitute an episcope of the sequence of the polypeptide encoded by SEQ ID No. 3.

Attorneys for Applicants emphatically disagree and respectfully submit that, for the reasons detailed below, this rejection is in error and must be withdrawn.

Zheng teaches a DNA sequence of an African mosquito, *Anopheles gambiae*. The sequence cited by the Office Action corresponds to residues 64-42 of the genomic DNA of *Anopheles gambiae*. The search results included in Office Action indicate that this portion of the *Anopheles* genomic DNA is from satellite DNA. Satellite DNA is not transcribed into protein and thus can not "inherently" encode a protein which constitutes an antigenic epitope of the protein encoded by SEQ ID NO:3.

Moreover, even if this fragment of the genomic DNA of Anopheles were derived from a coding region of the DNA molecule, it can not and does not "inherently " encode an antigenic epitope of the amino acid encoded by SEQ ID NO:3 since it is in the reverse polarity of SEQ ID NO:3. The amino acid encoded by residues 1270-1291 of SEQ ID NO:3 of the present specification corresponds to residues 424- 430 as indicated below.

SEQ ID NO:3 of the present application

5′ ACC CTT CAG ACA CAT ACC GAC AG 3′

Thr Leu Gln Thr His Thr Asp

The DNA taught by Zheng has residues

64 42

3′ ACC CTT CAG ACA CAT ACC GAC AG 5′

Since DNA is translated 5′ to 3′, the three theoretical amino acid sequences encoded by the three reading frames of residues 64-42 of Zheng are as follows:

42 64

5′ GAC AGC CAT ACA CAG ACT TCC CA 3′

Asp Arg His Thr Gln Thr Ser

5′ GA CAG CCA TAC ACA GAC TTC CCA 3′

Gln Pro Tyr Thr Asp Phe Pro

5′ G ACA GCC ATA CAC AGA CTT CCC A 3′

Thr Ala Ile His Arg Leu Pro

The complementary strand of the DNA fragment of Zheng and corresponding theoretical amino acid sequences are as follows:

64 42

5′ TGG GAA GTC TGT GTA TGG CTG TC 3′

Trp Glu Val Cys Val Trp Leu

5′ T GGG AAG TCT GTG TAT GGC TGT C 3′

Gly Lys Ser Val Tyr Gly Cys

5′ TG GGA AGT CTG TGT ATG GCT GTC 3′

Gly Ser Leu Cys Met Ala Val

Thus the allegation that Zheng's DNA comprising 64-42 of the genomic DNA of *Anopheles gambiae* "inherently" encodes an antigen epitope of the amino acid sequence of the polypeptide of SEQ ID NO:3 is not correct and plainly is in error.

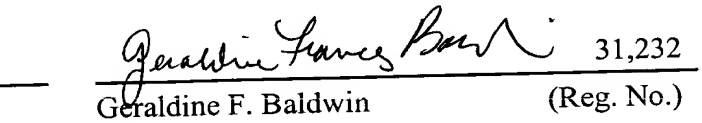
For all of the above reasons, the rejection of Claim 48 over Zheng be withdrawn.

In view of the above, it is submitted that all the rejections based on Section 102 are in error and must be withdrawn.

Further, it is submitted that the claims are in form for allowance and action to that end is requested.

Respectfully submitted,

Date October 23, 2001



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Appendix A

Marked-Up Version of the Specification
Application No: 09/388,090

[Double underlining indicates addition and strike-out (not square brackets) indicate deletion]

Page 3, line 9:

One object of this invention is to identify and provide a novel and highly conserved protein (referred to hereafter and in the claims as "NGSP") from *Neisseria spp.*, preferably *Neisseria gonorrhoeae*, *Neisseria ovis*, *Neisseria lacunata*, *Neisseria osloensis*, and *Neisseria bovis*. The protein of the present invention has a molecular weight of approximately 40-55 kD, and has limited similarity (~36% identity overall) to the DegP (HtrA) protein of *E. coli* [% identity determined using ~~TBLASTN~~ BLASTP program (Altschul et al., 1990, J. Molec. Biol. 215:403-10; Altschul et al., 1997, Nuc. Acids Res. 25:3389-3402) with data entered using FASTA format; expect 10 filter default; description 100, alignment ~~as described www.ncbi.nlm.nih.gov.~~] and has not been previously identified in any *Neisseria spp.* The protein sequence which is another object of this invention has similarity to several DegP/HtrA-like serine proteases from two other bacteria and these sequence homologies have not been previously reported for any *Neisseria spp.*

Page 10, line 15:

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al., 1990, J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison

purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. ~~See http://www.ncbi.nlm.nih.gov.~~ Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the CGC sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti (1994) *Comput. Appl. Biosci., 10*:3-5; and FASTA described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. 85*:2444-8. Within FASTA, ktup is a control option that sets the sensitivity and speed of the search. If ktup=2, similar regions in the two sequences being compared are found by looking at pairs of aligned residues; if ktup=1, single aligned amino acids are examined. ktup can be set to 2 or 1 for protein sequences, or from 1 to 6 for DNA sequences. The default if ktup is not specified is 2 for proteins and 6 for DNA. ~~For a further description of FASTA parameters, see http://bioweb.pasteur.fr/docs/man/man/fasta.1.html#sect2, the contents of which are incorporated herein by reference.~~

Appendix B

Marked-Up Version of the Amended Claims
Application No: 09/388,090

[Underlining indicates addition and square brackets indicate deletion]

37. (Twice Amended) An isolated [DNA] nucleic acid comprising a nucleotide sequence encoding an isolated [NGSP] non-cytosolic polypeptide of a *Neisseria* spp. (NGSP) polypeptide, which is a polypeptide of a Neisseria species with the proviso that said *Neisseria* species is not *N. meningitidis*, [and] which polypeptide has a molecular weight of about 40 kD to about 55 kD as determined in SDS polyacrylamide gel electrophoresis using glutamic dehydrogenase, carbonic anhydrase and myoglobin-blue as molecular weight markers, and which polypeptide has about 36% sequence identity to Deg P protein of *E.coli* when % sequence identity is determined using a BLASTP program using FASTA format, expect 10 filter default, description 100.

38. (Thrice Amended) An isolated [DNA having] nucleic acid comprising the sequence of SEQ ID NO. 3.

39. (Twice Amended) An isolated [DNA] nucleic acid encoding an NGSP polypeptide which comprises a nucleotide sequence that hybridizes at 68°C in 0.5M $NaHPO_4$ (pH 7.2) 1 mM EDTA/7% SDS or at 65°C in 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA or in 50% formamide/0.25 M $NaHPO_4$ (pH 7.2)/1 [0.25] mM NaCl/1 mM EDTA/7% SDS to the sequence of SEQ ID NO. 3 or the complement thereof, wherein said complement is complementary to at least 25 contiguous nucleotides of SEQ ID NO. 3.

50. (Once Amended) A pharmaceutical composition comprising the isolated [DNA] nucleic acid of any one of claims 37, 38, 39, 48 or 49.